

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
International application No. PCT/CA99/01207	Applicant's or agent's file reference 10662-83PCT
International filing date (day/month/year) 17 December 1999 (17.12.99)	Priority date (day/month/year) 18 December 1998 (18.12.98)
Applicant NANCI, Antonio et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
27 June 2000 (27.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

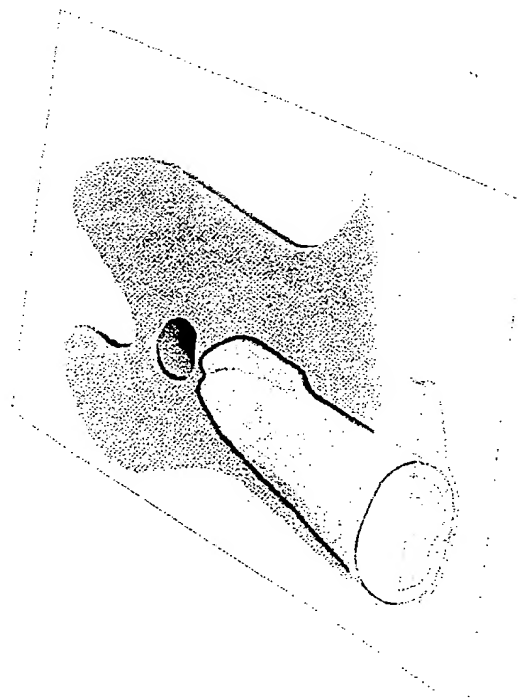
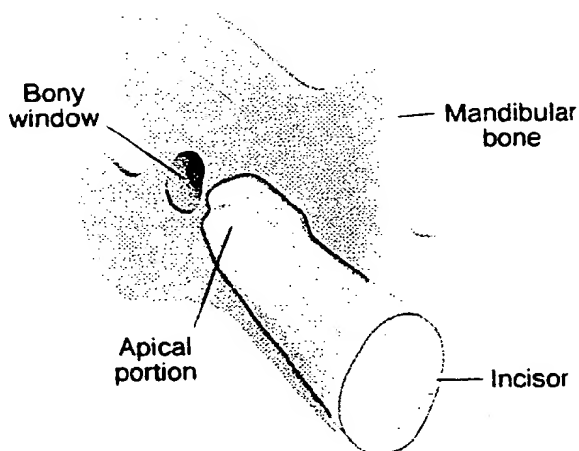
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Manu Berrod Telephone No.: (41-22) 338.83.38
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A01K 67/027, A61K 49/00, 48/00, G01N 33/00		A3	(11) International Publication Number: WO 00/36909
			(43) International Publication Date: 29 June 2000 (29.06.00)
(21) International Application Number: PCT/CA99/01207		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 17 December 1999 (17.12.99)		Published <i>With international search report.</i> (88) Date of publication of the international search report: 14 September 2000 (14.09.00)	
(30) Priority Data: 60/112,996 18 December 1998 (18.12.98) US			
(71) Applicant (for all designated States except US): UNIVERSITE DE MONTREAL [CA/CA]; 2900 Edouard-Montpetit, Montreal, Quebec H3T 1J4 (CA).			
(72) Inventors; and (75) Inventors/Applicants (for US only): NANJI, Antonio [CA/CA]; 9707 Ceres Street, Dollard-des-Ormeaux, Quebec H9B 3J3 (CA). VU, Duy-Dat [CA/CA]; 4562 Beaconsfield Street, Montreal, Quebec H4A 2H7 (CA). DANIEL, Nachaat, G. [CA/CA]; 6925 Messier Street, Brossard, Quebec J4Y 2G7 (CA).			
(74) Agents: COTE, France et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Quebec H3A 2Y3 (CA).			

(54) Title: IN VIVO ODONTOGENIC MODEL USING RODENT'S MANDIBULAR INCISOR



(57) Abstract

The present invention relates to the use of a rodent's mandibular incisor as an experimental model for the local and selective targeting of the odontogenic organ and its associated periodontal tissues. A surgical technique was developed to create a 'window' in the alveolar bone overlying the apex of the rodent incisor to allow direct diffusion of specific experimental agents. While direct deposition in the window is possible in some circumstances, an osmotic minipump is preferred to deliver the specific experimental agents in the window.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
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DE	Germany	LI	Liechtenstein	SD	Sudan		
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EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/01207

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A01K67/027 A61K49/00 A61K48/00 G01N33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCKEE MD, WARSHAWSKY H : "In vivo experimentation on rat incisor enamel organs through a surgical window. " ANAT REC;210(4):693-705, December 1984 (1984-12), XP000914347 cited in the application the whole document	1-14
Y	SUNDQUIST KT, MARKS SC JR. : "Bafilomycin A1 inhibits bone resorption and tooth eruption in vivo." J BONE MINER RES. 1994 OCT;9(10):1575-82., vol. 9, no. 10, October 1994 (1994-10), pages 1575-1582, XP000920946 cited in the application the whole document	1-14
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 June 2000

Date of mailing of the international search report

29/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chambonnet, F

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 99/01207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH, C.E. & Nanci A.: "A method for sampling the stages of amelogenesis on mandibular rat incisors using the molars as a reference for dissection" THE ANATOMICAL RECORD, vol. 225, 1989, pages 257-266, XP000920562 cited in the application the whole document	1
P,X	VU DD, DANIEL NG, Nanci A: "In vivo model for the experimental manipulation of calcified tissues: a surgical approach for accessing the odontogenic organ and associated tissues of the rat incisor." J HISTOCHEM CYTOCHEM, vol. 47, no. 3, March 1999 (1999-03), pages 323-326, XP000914310 the whole document	1-13

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

COTE, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montreal, Quebec H3A 2Y3
CANADASWABEY OGILVY RENAULT
MCGILL COLLEGE

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JUL 10 2000

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Date of mailing (day/month/year) 29 June 2000 (29.06.00)		IMPORTANT NOTICE	
Applicant's or agent's file reference 10662-83PCT			
International application No. PCT/CA99/01207	International filing date (day/month/year) 17 December 1999 (17.12.99)	Priority date (day/month/year) 18 December 1998 (18.12.98)	
Applicant UNIVERSITE DE MONTREAL et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,
OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
29 June 2000 (29.06.00) under No. WO 00/36909

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

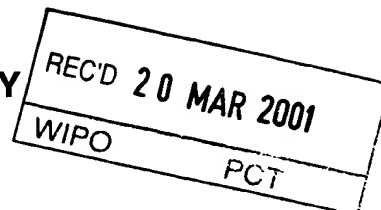
Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 10662-83PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA99/01207	International filing date (day/month/year) 17/12/1999	Priority date (day/month/year) 18/12/1998
International Patent Classification (IPC) or national classification and IPC A01K67/027		
Applicant UNIVERSITE DE MONTREAL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 27/06/2000	Date of completion of this report 16.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stolz, B Telephone No. +49 89 2399 8416 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01207

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-25 as originally filed

Claims, No.:

1-14 as received on 08/02/2001 with letter of 08/02/2001

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01207

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations see separate sheet

1. Reasoned statement

The amended set of claims meets the requirements of Art. 34(2)(b) PCT.

The claimed animal model, having a hole at specified positions of the mandibular bone, has not been described in the cited prior art. Consequently, the animal model and the claimed uses are new.

In comparison with the animal model described by McKee and Warshavsky (D1), the preparation of the present model seems to be less damaging to the underlying tissue. As the modification to the procedure of D1 in order to achieve this effect could not be derived from the cited prior art in an obvious way, the new animal model is deemed inventive.

WHAT IS CLAIMED IS:

1. An *in vivo* rodent model for testing of a compound in locally targeted odontogenic organ and associated periodontal tissues, comprising a mandibular incisor and a window in an alveolar bone overlying the incisor's apex or along radicular surface of the incisor, wherein said window is adapted for direct diffusion of a tested compound; and wherein a reduction in parameters consisting in histological, histomorphometric, eruption rate and matrix organization of said incisor compared to a normal incisor is indicative of a compound interfering with cellular or biochemical events involved in tissue formation of said incisor.
2. The model of claim 1, wherein said rodent is selected from the group consisting of rat, rabbit, mouse, hamster, guinea pig, squirrel and beaver.
3. The model of claim 1, wherein said window is further adapted to receive an osmotic pump for delivery of said tested compound.
4. A drug screening for a potential bone disease therapy compound, which comprises the steps of:
 - a) administering said compound to the model of claim 1;
 - b) determining histological and histomorphometric parameters of alveolar bone of the model's incisor and comparing to a normal incisor; wherein increase in anabolic activities or decrease in catabolic activities are indicative of a potential bone disease therapy compound.
5. The drug screening of claim 4, wherein said bone

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ART 84 ALIOT

disease is osteoporosis.

6. A drug screening for a compound inducing tissue repair, which comprises the steps of:

- a) administering said compound to the model of claim 1;
- b) determining histological and histomorphometric parameters of alveolar bone and other tissues of the model's incisor and comparing to a normal incisor; wherein increase in anabolic activities or decrease in catabolic activities are indicative of a compound inducing tissue repair.

7. The drug screening of claim 6, wherein said compound is a growth factor or a combination thereof.

8. A drug screening for a potential anti-cancer therapy compound, which comprises the steps of:

- a) administering said potential anti-cancer therapy compound to the model of claim 1,
- b) determining eruption rate of the model's incisor and comparing to normal eruption rate of an incisor; wherein a decrease in growth rate is indicative of a potential anti-cancer therapy compound in controlling cell division.

9. A test to determine the role of extracellular matrix molecules, which comprises the steps of:

- a) administering to the model of claim 1 using a minipump drugs that affect secretion and posttranslational modifications of said extracellular matrix molecules and/or antibodies or antagonists thereof;
- b) determining histological and histomorphometric parameters of alveolar bone and other tissues of

REPLACED BY
ART 34 AMDT

the model's incisor and comparing to a normal incisor; wherein cell organization and behavior, extracellular matrix organization, and degree of mineral deposition are indicative of a drug interfering with said extracellular matrix molecules.

10. A test for the immune response, which comprises the steps of:

- a) administering selected pathogens to the model of claim 1 using a minipump;
- b) determining growth profile of pathogen, tissue alterations, inflammatory cell infiltration are indicative of a pathogen inducing an immune response.

11. A test for toxicity of certain elements used for making biomaterials such as metals, which comprises the steps of:

- a) administering concentrations of metal ions to the model of claim 1 using a minipump;
- b) determining cell death, cell division and matrix production of the bone and tooth of the model's incisor and comparing to a normal incisor; wherein increase in anabolic activities or decrease in catabolic activities are indicative of a toxic metal.

12. A test for the efficiency of genetic material transfer, which comprises the steps of:

- a) administering an expression construct which encodes for a marker gene and/or a gene of interest to the model of claim 1 using a minipump;
- b) determining expression of said marker to assess

REPLACED BY
ART 34 AMDT

efficiency of said expression construct to transduce the tooth organ and associated tissues.

13. A method of gene therapy, which comprises the steps of:

- a) administering an expression construct which encodes for a gene of interest to the model of claim 1 using a minipump;
- b) inducing or repressing expression of a gene product of said gene.

14. A method of producing a non-human mammal knock-out model, whose germ cells and somatic cells are modified to express at least one gene or an allelic variant of said gene which comprises introducing an expression construct which encodes for a gene of interest or a deletion of said gene to the model of claim 1 using a minipump into the mammal, or an ancestor of the mammal, at an embryonic stage.

REPLACED BY
ART 34 AMDT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10662-83PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 99/ 01207	International filing date (day/month/year) 17/12/1999	(Earliest) Priority Date (day/month/year) 18/12/1998
Applicant UNIVERSITE DE MONTREAL et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

IN VIVO ODONTOGENIC MODEL USING RODENT'S MANDIBULAR INCISOR

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

3

☐ as suggested by the applicant.

☐ None of the figures.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/01207

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A01K67/027 A61K49/00 A61K48/00 G01N33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCKEE MD, WARSHAWSKY H : "In vivo experimentation on rat incisor enamel organs through a surgical window." ANAT REC;210(4):693-705, December 1984 (1984-12), XP000914347 cited in the application the whole document	1-14
Y	SUNDQUIST KT, MARKS SC JR. : "Bafilomycin A1 inhibits bone resorption and tooth eruption in vivo." J BONE MINER RES. 1994 OCT;9(10):1575-82., vol. 9, no. 10, October 1994 (1994-10), pages 1575-1582, XP000920946 cited in the application the whole document	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 June 2000

Date of mailing of the international search report

29/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Fax: (+31-70) 340-3016

Authorized officer

Chambonnet, F

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 99/01207

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH, C.E. & NINCI A.: "A method for sampling the stages of amelogenesis on mandibular rat incisors using the molars as a reference for dissection" THE ANATOMICAL RECORD, vol. 225, 1989, pages 257-266, XP000920562 cited in the application the whole document	1
P, X	--- VU DD, DANIEL NG, NINCI A: "In vivo model for the experimental manipulation of calcified tissues: a surgical approach for accessing the odontogenic organ and associated tissues of the rat incisor." J HISTOCHEM CYTOCHEM, vol. 47, no. 3, March 1999 (1999-03), pages 323-326, XP000914310 the whole document -----	1-13